

# The Quest for Precision Medicine: A Metabolic Approach

Demystifying Medicine

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# Concept of a Disease “Cure”

- Penicillin – Pneumococcal pneumonia
- Vaccines – Eradication of polio in the US, and smallpox in the world
- Duodenal Ulcer – H2 blockers and proton pump inhibitors (excellent treatment, but do they treat the etiologic basis of the disease?)

No – specific treatment of H. Pylori actually eradicates the cause of the disease

# Discovery of Etiologic or Pathophysiologic Basis of Metabolic Diseases

# Etiologic Basis of Conditions

- Hypertension
- Dyslipidemia
- Diabetes

Known roughly 10-15%.  
Thus therapy is largely nonspecific.

# Diabetes – A Metabolic Disease

## Classifications:

- Type 1 ( $\beta$ -cell destruction, usually leading to absolute insulin deficiency), 5-10%
- Type 2, (Insulin resistance with relative insulin deficiency), 90-95%
- Other Specific Types
- Gestational

# Insulin Resistance Spectrum

Least Severe

Most Severe

## Common forms

- Metabolic Syndrome

- Polycystic Ovarian Syndrome

- Type 2 Diabetes

## Syndromic Forms

- Lipodystrophy

- Insulin Receptor Mutations

- Type B insulin resistance

# Lipodystrophy Syndromes

- Heterogeneous group of disorders characterized by selective loss of adipose tissue



# The Insulin Receptoropathy

- Acquired

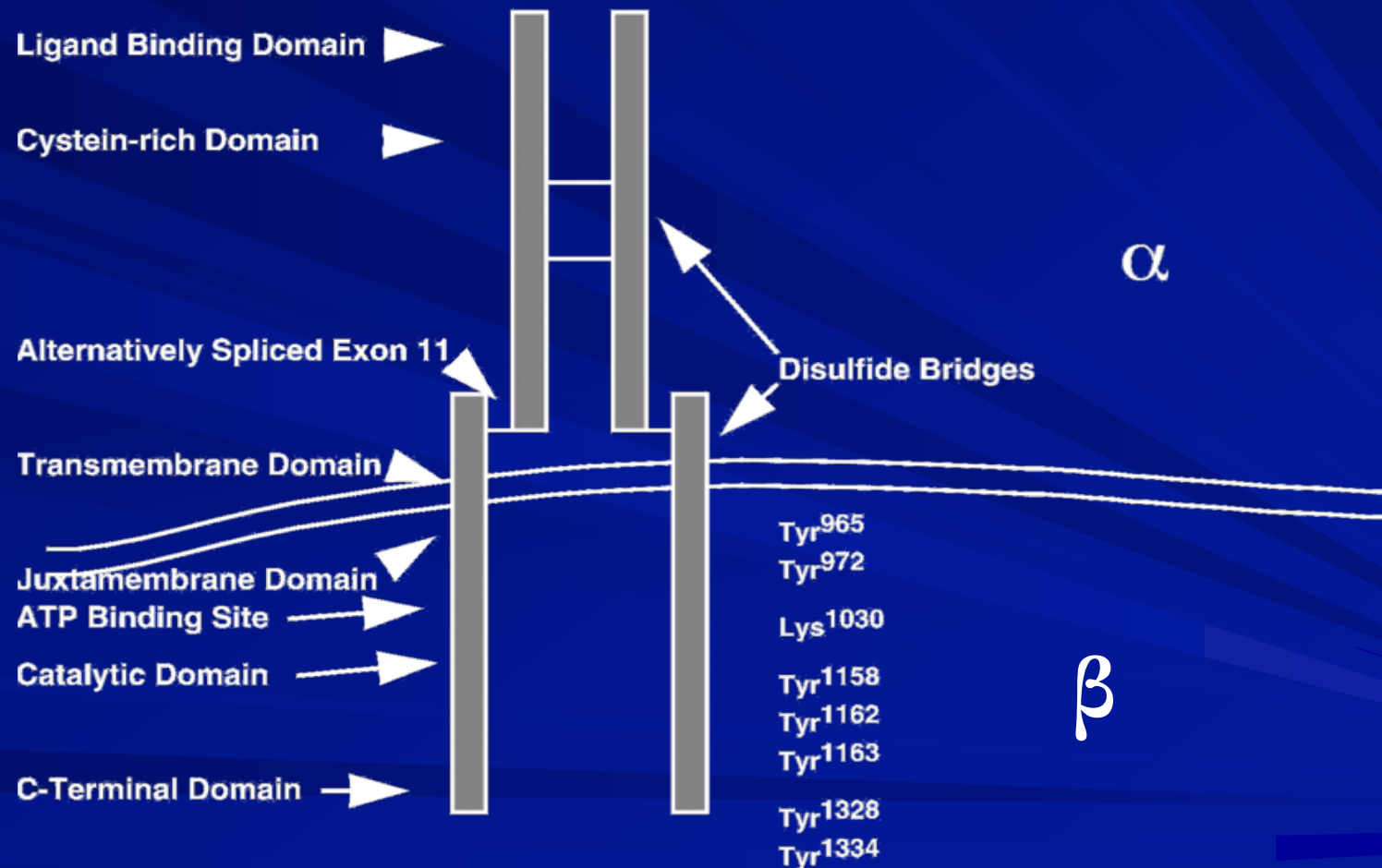
- Autoantibodies to the insulin receptor

- Genetic

- Mutations of the insulin receptor



# Insulin Receptor Structure



# The Clinical Challenge

## Three Stories:

- Development of new technology.
- New use of existing technology.
- Combinations of the old and the new.

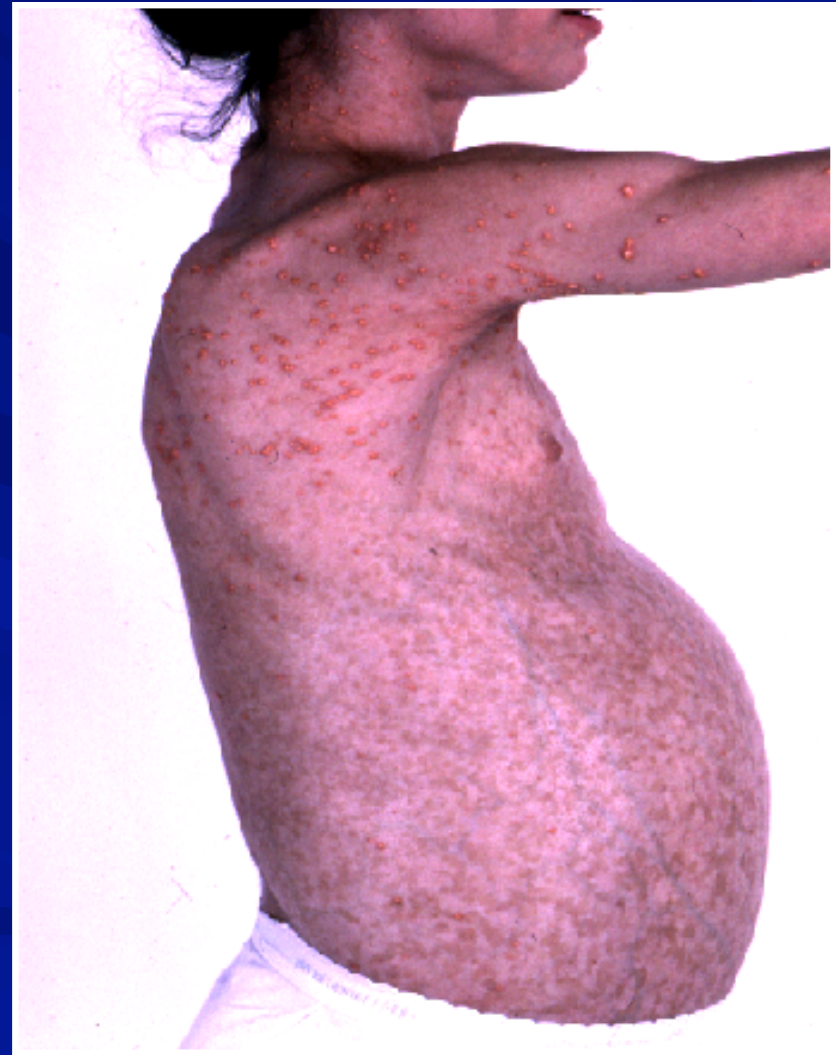
# The Clinical Challenge

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# Lipodystrophy Syndromes

- Paucity of fat
- Deficiency of adipocyte hormones (e.g. leptin)
- Insulin resistance
- Hypertriglyceridemia
- Fatty infiltration of liver and other tissues



This story begins with an obese mouse...

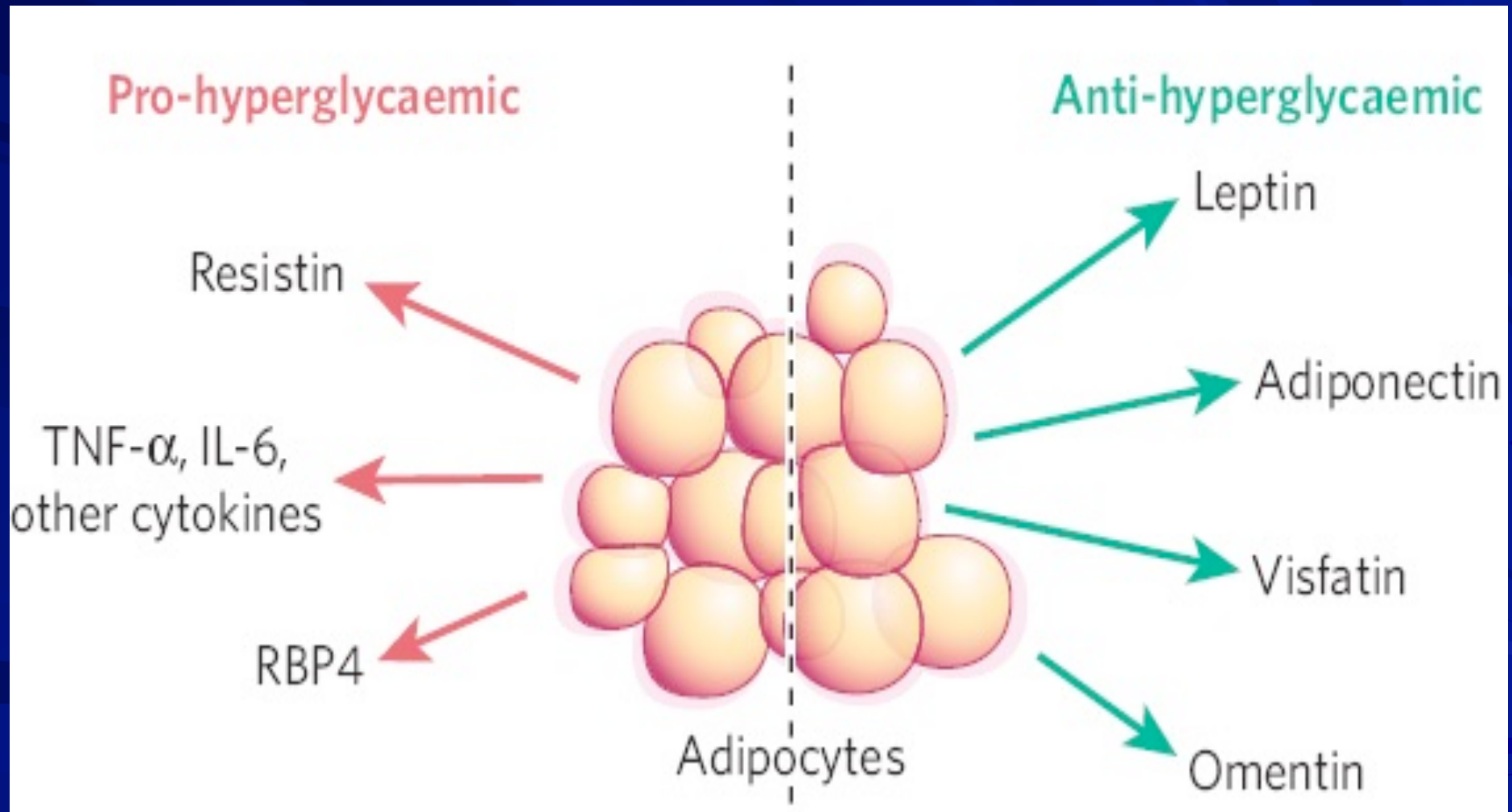




# Leptin

- Leptin is the major hormone regulating energy balance
- Plasma leptin concentration is a function of adiposity.
- In obesity plasma leptin is elevated and leptin administration has little effect in regulating energy intake.

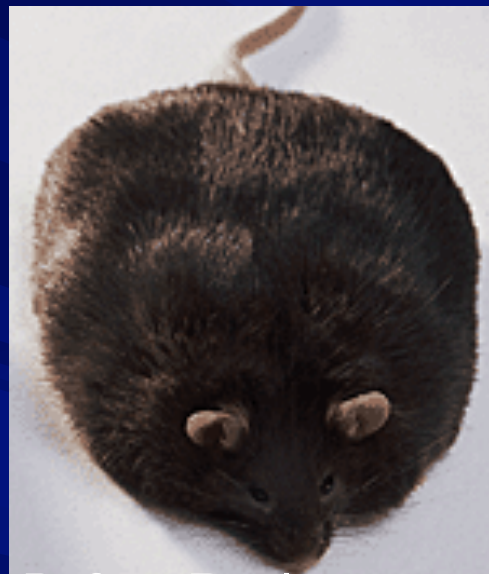
# Adipose Tissue as an Endocrine Organ and Regulators of Glucose Homeostasis



# Leptin: From Hormone to Major Pharmaceutical



# Leptin: Of Mice and Man

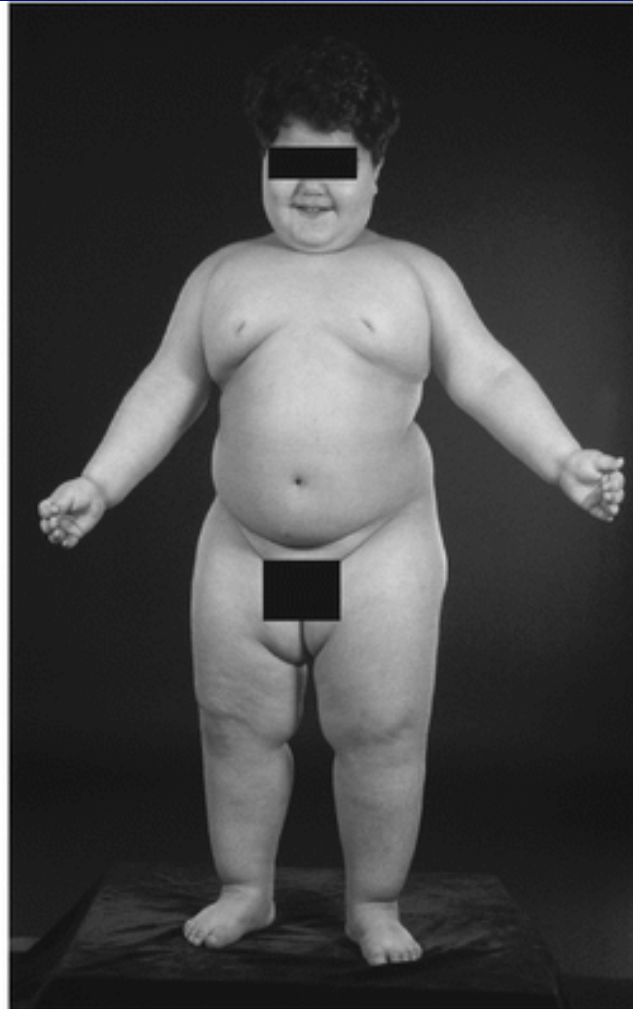


Before Replacement



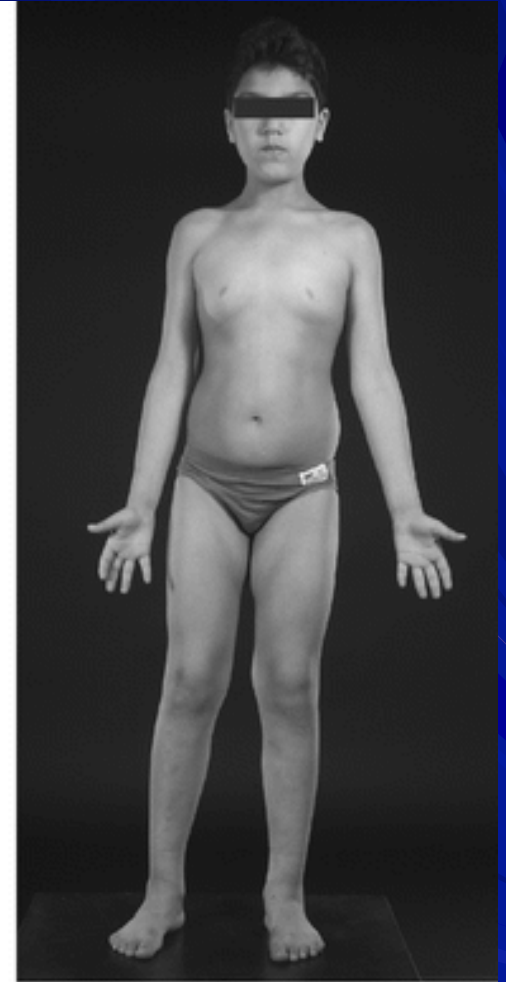
After Replacement

(a)



3-year-old weighing 42 kg

Before Replacement



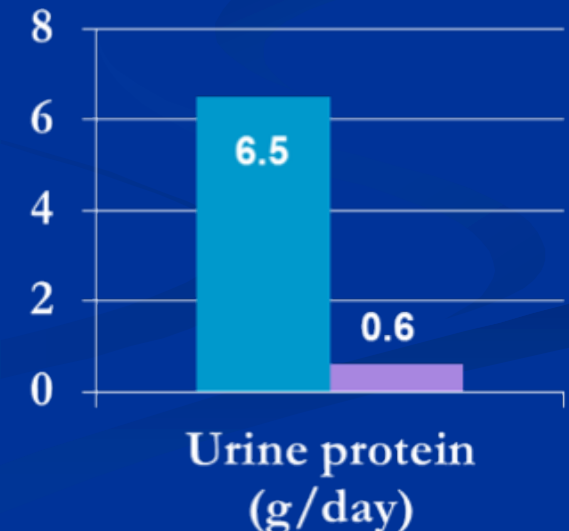
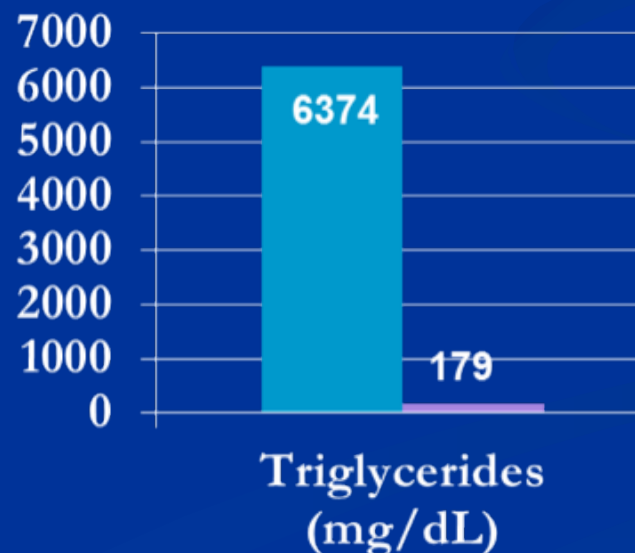
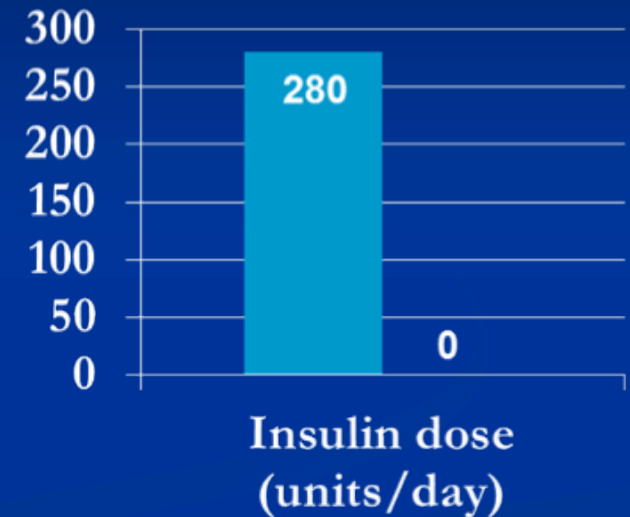
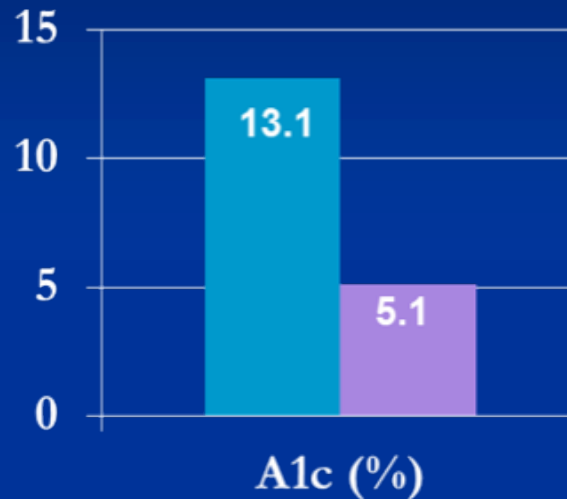
7-year-old weighing 32 kg

After Replacement

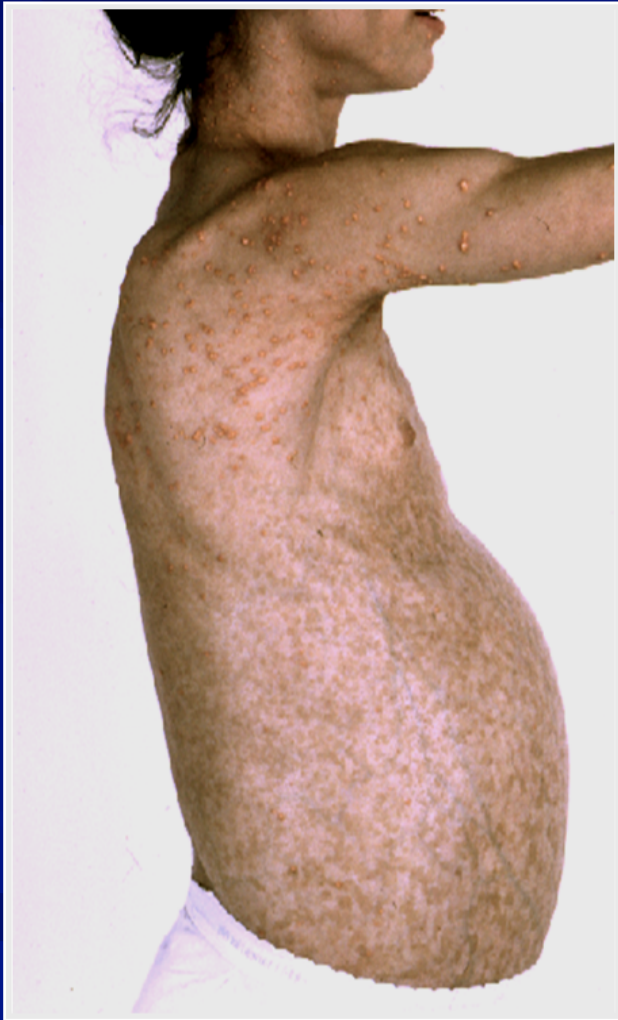
*Farooqi S. NEJM, September 1999*

# Dramatic Effects of Leptin

- 21 year old woman with generalized lipodystrophy
- Poorly controlled diabetes with h/o DKA
- Severe hypertriglyceridemia
- Nephrotic range proteinuria



**Before  
Leptin**



**1 year on  
Leptin**



# FDA review

■ Based on the NIH data, metreleptin was approved for patients with generalized lipodystrophy, with or without metabolic complications

■ Not approved for partial lipodystrophy, regardless of metabolic disease

## -----INDICATIONS AND USAGE-----

MYALEPT is a leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. (1)

### Limitations of Use

- The safety and effectiveness of MYALEPT for the treatment of complications of partial lipodystrophy have not been established. (1)
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established. (1)
- MYALEPT is not indicated for use in patients with HIV-related lipodystrophy. (1)
- MYALEPT is not indicated for use in patients with metabolic disease, without concurrent evidence of generalized lipodystrophy. (1)



# The Clinical Challenge

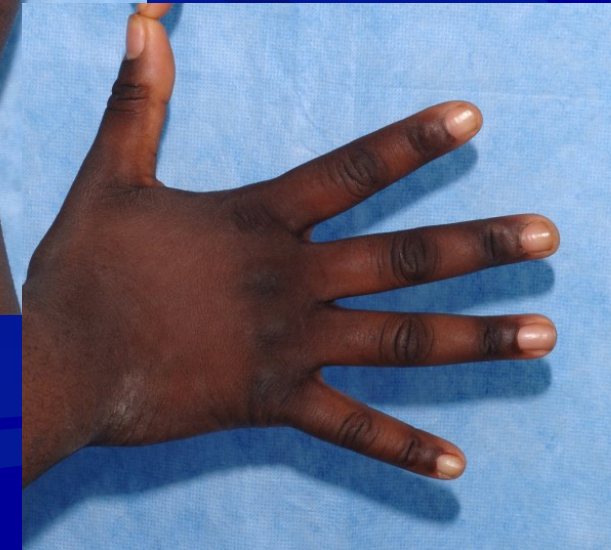
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# The patient

- 21 year old African American female
- Average Fasting blood glucose: 371 mg/dL
- Extreme weight loss
- Massive polyuria (Up to 15 liters urine/day)
- Acanthosis nigricans
- Extreme insulin resistance







# Strategy of Therapeutic Approach

- Goal: elimination of the autoantibody
- Rituximab: antibody against CD-20, a cell surface molecule expressed by B-cells
- High dose pulsed steroids: to reduce pre-existing antibody-producing plasma cells
- Non-specific T-cell directed immunosuppression
  - Cyclophosphamide
  - Cyclosporine



# Our Type B Insulin resistance patient after treatment



# The Clinical Challenge

## Three Stories:

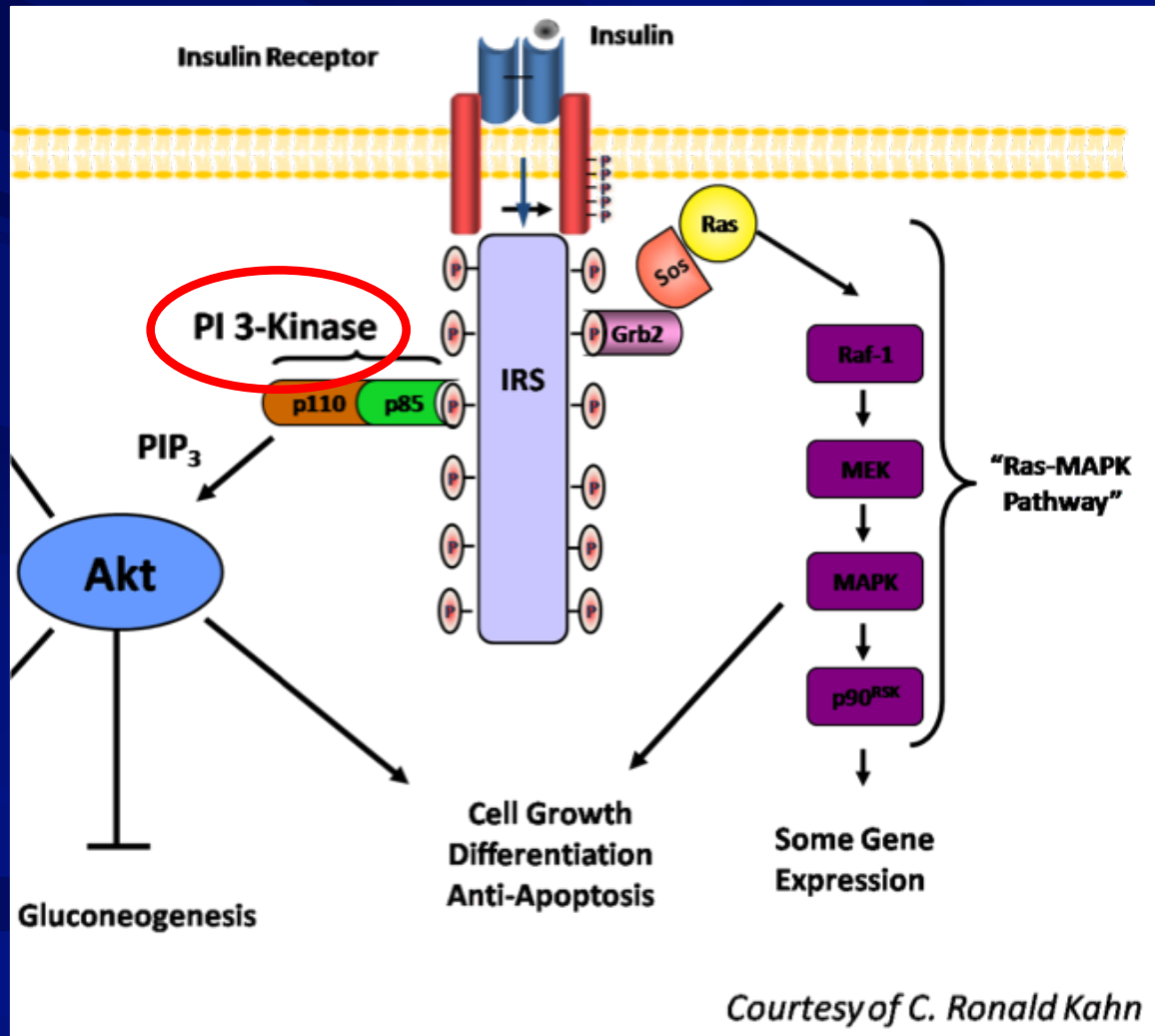
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# Patient

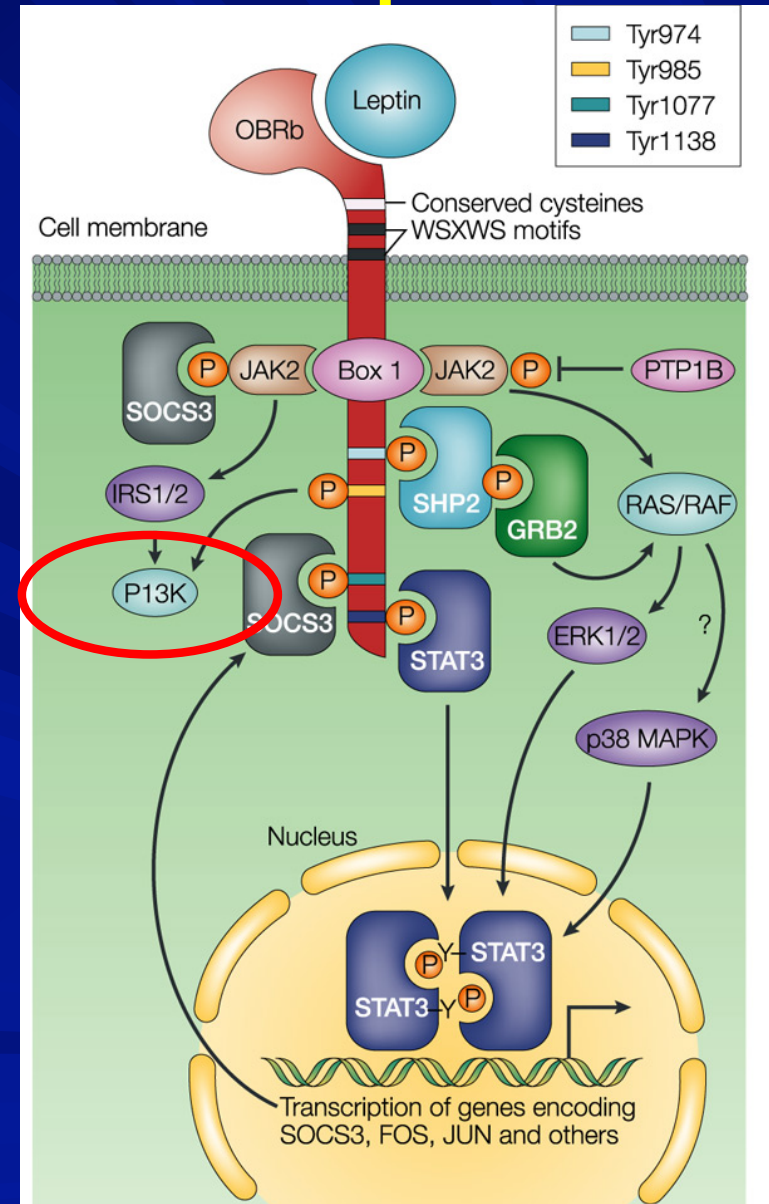
- 12 year old Korean male
- At age 8 months of age presented with:
  - Extreme Hyperinsulinemia
  - Acanthosis nigricans
  - Increased body hair
  - Abnormal dentition
- At age 9 years old → Diabetes → A1c 11.8%



# Insulin



# Leptin





# Insulin Resistance Spectrum

Least Severe

Most Severe

## Common forms

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- Polycystic Ovarian Syndrome

- Type 2 Diabetes

## Syndromic Forms

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